

**REMARKS/ARGUMENTS**

Applicants have amended the Specification to correct typographical errors. Applicants have amended Claims 1, 2, 7, 9-12, 16, 26-27, 32, 34-37, 41 and 48-49. Support for the amendments may be found, for example in the originally filed claims and on pages 3-5 of the Specification. Claims 9-12, 34-37 and 48-49 have been amended to clarify that it is the "consensus sequence(s)" that overlap the genomic space. Claims 7 and 32 have been amended to correct their respective dependencies.

Applicants submit that no new matter is presented in these amendments and respectfully request entry of the same. By these amendments, Applicants do not acquiesce to the propriety of any Examiner's rejections and do not disclaim any subject matter to which they are entitled.

***Rejections under 35 U.S.C. § 101 should be withdrawn***

The Examiner has rejected Claims 1-12, 16-17, and 19-24 under 35 U.S.C. § 101 for allegedly being directed under non-statutory subject matter. Applicants respectfully disagree and traverse this rejection.

The Office Action alleges that the steps recited in the methods of Claims 1-12 are limited to data manipulation and do not result in a useful, concrete and tangible result. Specifically, the Office Action alleges that the cluster has no tangible, concrete and useful application. Applicants respectfully disagree with the Office Action. Transcript clustering is a well known methodology to assemble transcript sequences for the generation and analysis of gene expression array. Moreover, Applicants wish to clarify

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that the modified cluster has a tangible, concrete and useful application since it identifies transcripts that represents the same gene and remove transcript sequences comprising poorly aligned regions or regions that do not align to the corresponding genomic sequence (e.g. pages 4-5 and pages 18-21 of the specification).

The Office Action alleges the steps recited in Claims 16-24 are limited to data manipulation and do not result in a useful, concrete and tangible result. Specifically, the Examiner alleges that there is no step that designs the array, the final step being selecting the probes intended to be used in designing the array. Applicants respectfully disagree with the Office Action. As described, for example, in page 17 of the Specification (under the section heading "Nucleic Acid Probe Array Design Process"), a nucleic acid design process involves selecting the target sequences and selecting the probes. Claim 16 includes a step of selecting the target sequences by aligning a plurality of transcript sequences in a cluster to their corresponding genomic sequence, modifying the clusters according to their alignment to the genomic sequence to obtain at least one modified cluster and a step of selecting the probes targeting the at least one modified cluster. As described in the Specification, the probe sequences can then be translated to photolithographic masks, command for controlling ink-jet directed synthesis or soft lithographic synthesis process (page 17 of the Specification). This is well known in the art and taught in the specification and in numerous patent documents cited in the specification. In addition, the Examiner alleges that the claims do not indicate that the cluster has any tangible, concrete and useful application. Applicants respectfully disagree. As stated above and on Page 18 of the Specification, each cluster identifies

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transcripts (or ESTs sequences) that represent the same gene and removes low quality regions of transcripts sequences.

In summary, in view of the above remarks and amendments, Applicants respectfully submit that the rejection of Claims 1-12, 16-17 and 19-24 under 35 U.S.C. § 101 should be withdrawn.

***Rejections under 35 U.S.C. § 112 should be withdrawn***

Claims 1-12, 16-17, 19-24, 26-37, 41-42 and 44-49 have been rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully disagree with the Office Action.

Specifically, the Office action alleges that the steps of determining the quality of the clusters according to the alignment and modifying the clusters according to the determined quality of Claims 1 and 26 present new matter. Applicants respectfully disagree with the Office Action. The Examiner's attention is directed to page 4 and page 20 of the Specification. Particularly, page 4 of the Specification teaches that the methods of the invention "include aligning the transcript sequences with genomic sequences. Given these alignments, cDNA sequence quality as well as whether the clusters need to be modified can be determined according to the alignments." Therefore, the specification provides ample support for the step of determining the quality of the cluster and modifying the cluster and this rejection under 35 U.S.C §112, first paragraph, should be withdrawn.

In addition, the Office action alleges that the specification does not disclose that classification of a cluster as chimeric is a determination of the quality of the clusters as

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implied by the way claims 2-12 and 27-37 are written. Applicants respectfully disagree. For example, page 20 of the Specification teaches in great details how a cluster is assessed in view of its alignment to the genomic sequence i.e. after alignment, clusters are sorted out into unaligned clusters, cleanly aligned clusters or chimeric clusters. Therefore, Applicants respectfully submit that the rejection of Claims 2-12 and 27-37 should be withdrawn.

In addition, the Office Action alleges that the specification does not contemplate that the selection of the probes alone results in designing a nucleic acid probe array as stated in Claims 16 and 41. Applicants respectfully disagree and wish to direct the Examiner's attention to page 17 of the Specification, paragraph heading "Nucleic Acid Probe Array Design" that teaches in details how a nucleic acid array is designed. More specifically, a nucleic acid array is designed by selecting target sequences (i.e. modified clusters in Claims 16 and 41) and selecting probes for detecting the target sequences. This is well known in the art and taught in the specification and in numerous patent documents cited in the specification. Therefore, Applicants respectfully submit that this rejection should be withdrawn.

Claims 1-12, 16-17, 19-24, 26-37, 41-42 and 44-49 are rejected under 35 U.S.C. §112, first paragraph, by the Examiner for allegedly lack of enablement. Applicants respectfully disagree with the Office Action and submit that the rejected claims are fully enabled.

The Office Action alleges that the method as written in Claims 1-12 does not provide guidance on how quality is determined based upon any alignment. Applicants respectfully submit that pages 4-5 and page 20 of the Specification teach in great details

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that poorly aligned regions or regions which do not align with corresponding genomic sequences can be treated as low quality ("bad") while the aligned portion can be treated as high quality ("good"). For example, it is taught in page 20 of the Specification how the alignment of each sequence cluster is assessed in view of the genomic information. Clusters are then sorted into different categories such as cleanly aligned, unaligned and chimeric clusters (i.e. clusters where the member sequences align to two or more positions). The Examiner further notes that there is no guidance as to how to modify the cluster based upon a particular quality determination. Applicants respectfully submit that pages 5 and 20 of the Specification, Figure 4 and Claims 7-12 for example, teach in great details that the steps of modifying may include subclustering chimeric clusters and merging the clusters with consensus which overlap in the genomic space. For example, chimeric clusters may need to be modified by subclustering until no chimeric cluster is detected (see, Claim 8, for example).

The Office Action alleges that the method as written in Claims 16-17 and 19-24 does not provide sufficient positive, active steps to practice the method. Specifically, the Office Action alleges that Claim 16 does not have design steps nor result in a design for a nucleic acid probe array. Applicants respectfully submit that it is well known in the art and also taught in the specification (for example, page 17) that a nucleic acid probe array design involves selecting the target sequences (i.e. aligning and modifying steps of Claim 16) and selecting the probes (i.e. selecting step of Claim 16). The Examiner further notes that there is no guidance on how to determine whether the clusters need to be modified and what type of modification to make. Applicants wish to direct the Examiner's attention to pages 5 and 20 of the Specification, Figure 4 and Claims 17-24, for example,

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that teach in great details that the steps of modifying may include subclustering chimeric clusters and merging the clusters with consensus which overlap in the genomic space. In addition, the Office Action alleges that the claims and specification do not provide any criteria by which the probes are selected. Applicants respectfully submits that it is well known in the art and it is taught in pages 12 and 17 of the Specification and in Claim 16 that probes targeting at least one modified cluster are selected to design a nucleic acid probe array.

Applicants therefore submit that the method of Claims 1-12, 16-17, 19-24, and the corresponding computer readable medium comprising computer executable code to perform the method of Claims 26-37, 41-42 and 44-49 are fully enabled by the Specification. Applicants respectfully request that Claims rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Claims 1-12, 16-17, 19-24, 26-37, 41-42 and 44-49 are rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner alleges that the criteria by which the quality determination is made in Claims 1 and 26 remain incomplete and confusing. Applicants respectfully disagree. Claim 1 teaches that the quality of the cluster is determined according to the alignment of the transcript sequences in the cluster with their corresponding genomic sequences. It is well known in the art and taught in the specification that a high quality cluster includes sequences that align to their corresponding genomic sequences. The Examiner further points out that the metes and bound of "modifying" is not known. Applicants have

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amended Claims 1 and 26 to recite "modifying ...to improve alignment quality". Support for this amendment may be found on pages 3-5 of the Specification. Applicants respectfully submit that no new matter is entered by this amendment.

The Examiner alleges that Claims 7 and 32 remain confusing. Applicants have amended Claims 2 and 27 upon which Claims 7 and 32 depend to recite "the step of determining further comprises...". Claims 7 and 32 have been amended to clarify that it is the sequences within the clusters that are realigned. Applicants respectfully submit that no new matter is entered by these amendments.

Claim 16 is allegedly incomplete for failing to provide the stated goal of preamble. Applicants respectfully disagree. It is well known in the art and taught in numerous patent documents cited in the specification that the probes detecting target sequences are selected to design a nucleic acid probe array. Probe sequences may then be translated to photolithographic mask, commands for ink-jet directed synthesis, or soft lithographic synthesis process (see, Page 17 of the Specification, under "Nucleic acid probe array design process" heading).

Claim 16 and 41 are allegedly confusing in reciting "modifying the clusters according to their aligning to the genomic sequence to obtain at least one modified cluster" for not setting forth the positive and active steps that must be taken. Claims 16 and 41 have been amended to recite "modifying the clusters' sequences that are not optimally aligned to the genomic sequence to obtain at least one modified cluster wherein the modified cluster's sequence display an improved alignment to said genomic sequence". Therefore, Applicants respectfully submit that Claim rejection be withdrawn.

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In view of the above amendments and remarks, Applicants respectfully submit that Claims rejection under 35 U.S.C. 112, second paragraph, should be withdrawn.

Applicants assert that no new matter is presented by these amendments and respectfully request entry of the same.

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**CONCLUSION**

For these reasons, Applicants believe all pending claims are now in condition for allowance. If the Examiner has any questions pertaining to this application or feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5000.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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